PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
SCB643PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 01/08756	27/07/2001	28/07/2000
Applicant		
PICCONE, Lorenzo		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   APPARATUS FOR THE TREATMENT OF VASCULAR AND ORTHOPEDIC DISORDERS BY APPLICATION OF ELECTRICAL PULSES TO THE SKIN TO MODULATE THE NEURO-VEGETATIVE SYSTEM

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

An apparatus for the treatment of vascular and/or muscle and/or tendon disorders and/or to increase the production of VEGF, comprises: means designed to generate electrical pulse series having a width from 10 to 40 usec and intensity from 100 to 70 uAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec, and a voltage up to 220 Volts; means designed to apply the said pulses to a patient through the epidermis; means designed to evaluate the tissue reaction; means designed to vary the said pulses on the basis of the tissue reaction detected; at least one which means can be controlled by the patient/user.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP01/08756

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 725 563 A (KLOTZ ANTOINE) 10 March 1998 (1998-03-10) the whole document ---	1-6, 11-13
Y	US 4 505 275 A (CHEN WU) 19 March 1985 (1985-03-19) the whole document ---	1-6, 11-13
A	US 5 395 398 A (ROGOZINSKI WALLACE J) 7 March 1995 (1995-03-07) the whole document ---	1-6,8, 11-13
A	US 5 018 521 A (CAMPBELL WILLIAM P) 28 May 1991 (1991-05-28) the whole document ---	1-6, 11-13
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2002	22/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ferrigno, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/E[redacted]1/08756

C.(Continuation) DOCUMENTS CONSIDERED TO [redacted]ELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 064 911 A (WINGROVE ROBERT C) 16 May 2000 (2000-05-16) the whole document -----	1-6, 11-13

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/E[redacted]1/08756

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5725563 A	10-03-1998	FR 2704151 A1	28-10-1994
		AT 188388 T	15-01-2000
		AU 6572794 A	08-11-1994
		DE 69422511 D1	10-02-2000
		DE 69422511 T2	31-08-2000
		EP 0696215 A1	14-02-1996
		ES 2144050 T3	01-06-2000
		WO 9423791 A1	27-10-1994
		JP 8508897 T	24-09-1996
US 4505275 A	19-03-1985	NONE	
US 5395398 A	07-03-1995	NONE	
US 5018521 A	28-05-1991	AU 4627289 A	28-05-1990
		CA 2002405 A1	08-05-1990
		DE 68927258 D1	31-10-1996
		DE 68927258 T2	24-04-1997
		EP 0396720 A1	14-11-1990
		WO 9004955 A1	17-05-1990
US 6064911 A	16-05-2000	NONE	

10/070 949

Copy for the Elected Office (EO/US)

PCT/EP01/08756

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

MINOJA, Fabrizio
Bianchetti Bracco Minoja S.r.l.
Via Rossini, 8
I-20122 Milan
Italy

Date of mailing (day/month/year)
19 September 2002 (19.09.02)

Applicant's or agent's file reference
SCB643PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/08756

International filing date (day/month/year)
27 July 2001 (27.07.01)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
PICCONE, Lorenzo
Via La Pira, 10
I-40100 Bologna
Italy

State of Nationality: IT
State of Residence: IT
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
LORENZ BIOTECH S.P.A.
Viale Berti Pichat 10
I-40127 Bologna
Italy

State of Nationality: IT
State of Residence: IT
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
The company in Box 2 should be added to the record as applicant for all States except US. The person in Box 1 is now applicant/inventor for US ony. A power of attorney from the applicant in Box 2 is required.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Laurence GALLAY

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

005126143

Copy for the Elected Office (EO/US) PCT/EP01/08756

PATENT COOPERATION TREATY 10/070 949

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

LUPPI, Luigi
Luppi & Crugnola S.R.L.
Viale Corassori, 54
I-41100 Modena
Italy

Date of mailing (day/month/year)
20 March 2003 (20.03.03)

Applicant's or agent's file reference
SCB643PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/08756

International filing date (day/month/year)
27 July 2001 (27.07.01)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
LORENZ BIOTECH S.P.A.
Viale Berti Pichat, 10
I-40127 Bologna
Italy

State of Nationality: IT
State of Residence: IT
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
LORENZ BIOTECH S.P.A.
Via Statale 12 Sud, 109
I-41036 Medolla (MO)
Italy

State of Nationality: IT
State of Residence: IT
Telephone No.:
Facsimile No.:
Teleprinter No.:

RECEIVED JUN 16 2003 TC 3700 MAIL ROOM

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
Marie-José DEVILLARD (Fax 338-8995)

Telephone No. (41-22) 338 9439

Form PCT/IB/306 (March 1994) 005533487

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

LUPPI, Luigi
Luppi & Crugnola S.R.L.
Viale Corassori, 54
I-41100 Modena
Italy

Date of mailing (day/month/year)
18 March 2003 (18.03.03)

Applicant's or agent's file reference
SCB643PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/08756

International filing date (day/month/year)
27 July 2001 (27.07.01)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
MINOJA, Fabrizio
Bianchetti Bracco Minoja S.r.l.
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Facsimile No.: +39.02.783078
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
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Luppi & Crugnola S.R.L.
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I-41100 Modena
Italy

State of Nationality:
State of Residence:
Telephone No.: +39.059 359916
Facsimile No.: +39.059 359226
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
Marie-José DEVILLARD (Fax 338-8995)

Telephone No. (41-22) 338 9439

10/070949

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB643PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP01/08756	27/07/2001	28/07/2000
International Patent Classification (IPC) or national classification and IPC A61N1/36		
Applicant LORENZ BIOTECH S.P.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/02/2002	11.10.2002
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Ferrigno, A Telephone No. +31 70 340 2174

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/08756

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-13 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/12-12/12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 14-16.

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-13

	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 14-16 relates to a method for treatment of human body by therapy. Article 34(4) (a) (i) and Rule 67.1 (iv) PCT.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US-A-5 725 563 (KLOTZ ANTOINE) 10 March 1998 (1998-03-10)
D2: US-A-4 505 275 (CHEN WU) 19 March 1985 (1985-03-19)
D3: US-A-5 395 398 (ROGOZINSKI WALLACE J) 7 March 1995 (1995-03-07)
D4: US-A-5 018 521 (CAMPBELL WILLIAM P) 28 May 1991 (1991-05-28)
D5: US-A-6 064 911 (WINGROVE ROBERT C) 16 May 2000 (2000-05-16)

1) Preliminary observation: according to Article 6 PCT the matter for which protection is sought is defined by the claims. Hence the opinion on novelty and inventive step is based on the subject-matter defined by the claims. The subject-matter defined in claim 1 of the present Application includes various alternative possibilities generated by to the term "and/or". Document D1 discloses an apparatus suitable for one of the alternative possibilities. In fact D1 discloses an apparatus for the treatment of vascular and/or muscle and/or tendon disorders.

1.1) Hence, D1 discloses an apparatus for the treatment of vascular and/or muscle and/or tendon disorders (cf. col. 1, lines 5-18) comprising:
- means designed to generate electrical pulses /cf. col. 3, lines 44-46);
- means 2,3,4 designed to apply said pulses to a patient through the epidermis;
- means designed to evaluate the tissue reaction (cf. col. 2, lines 41-48);
- means designed to vary the said pulses on the basis of the tissue reaction detected (cf. col. 2, lines 8-15);

at least one of which means can be controlled by the patient/user (cf. col. 3, lines 44-54).

1.2) Hence, the subject-matter of claim 1 differs from the disclosure of D1 only in the numerical values of the specified parameters.

1.3) There are other differences between the disclosure of D1 and the disclosure of the present Application: for instance in D1 an impedance measurement is carried out, which is absent in the present Application; this is however not apparent from the definition of invention given in claim 1 and the sole difference between the subject-matter of claim 1 and the disclosure of D1 resides only in the numerical values of the specified parameters.

1.4) The above-mentioned difference is not considered inventive for the following reasons.

D1 discloses values having the same order of magnitude as those recited in claim 1; furthermore, as for the present Application, D1 varies the parameters of the pulses on the basis of the tissue reaction detected.

D2 discloses also an electrical stimulator wherein a broad range of controllable values is refined according to the result of the treatment.

Hence, the range of values defined in claim 1 is just an obvious design option that the skilled person would select, without the exercise of inventive skill.

2) The additional features of dependent claims 2-13 are just some of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/09809 A1

(51) International Patent Classification[7]: A61N 1/36

(21) International Application Number: PCT/EP01/08756

(22) International Filing Date: 27 July 2001 (27.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
M12000A 001733 28 July 2000 (28.07.2000) IT

(71) Applicant and
(72) Inventor: **PICCONE, Lorenzo** [IT/IT]; Via La Pira, 10, I-40100 Bologna (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milan (IT).

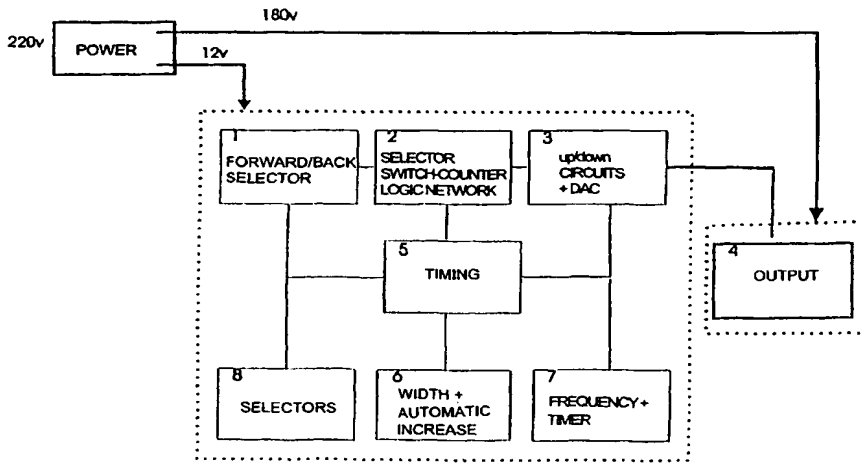
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** APPARATUS DESIGNED TO MODULATE THE NEUROVEGETATIVE SYSTEM AND INTEGRATE ITS ACTION WITH THAT OF THE CENTRAL NERVOUS SYSTEM; APPLICATIONS IN THE TREATMENT OF THE VASCULAR SYSTEM AND ORTHOPAEDIC DISORDERS



(57) **Abstract:** This invention relates to a new type of apparatus designed to modulate the neurovegetative system and integrate the neurovegetative action with that of the central nervous system. The method is not invasive, because it uses pulses transmitted through the skin;the intensity of the stimulus is controlled directly by the patient in order to achieve better integration with the central nervous system. This invention effectively treats vascular disorders resulting from obstruction of the arteries of the legs, heart and brain because it induces vasodilatation and increases blood flow and the production of new blood vessels. The method also improves lesions of the spinal column, especially those affecting the back and neck, and other orthopaedic disorders.

WO 02/09809 A1

APPARATUS DESIGNED TO MODULATE THE NEUROVEGETATIVE SYSTEM AND INTEGRATE ITS ACTION WITH THAT OF THE CENTRAL NERVOUS SYSTEM; APPLICATIONS IN THE TREATMENT OF THE VASCULAR SYSTEM AND ORTHOPAEDIC DISORDERS

Purpose of invention

This invention relates to apparatus and an innovative method designed to regulate the function of the neurovegetative system and integrate it with that of the central nervous system. This effect is achieved by administering electrical pulses to the skin, the intensity of the pulses being controlled directly by the patient.

The new method induces vasodilatation, stimulates neoangiogenesis and increases blood flow. The regulation of the vascular flow obtained with the new technology allows treatment of vascular diseases involving organic obstruction of the arteries, which often affect the lower limbs, heart and brain. The new technology also allows effective treatment of disorders of the spinal column, especially the neck and the lumbosacral area.

The same apparatus can be effectively used to treat many other orthopaedic disorders, for example inflammation and proprioceptive sensory alterations caused by damage to the muscolar and articular system.

Basis of the invention

Atherosclerosis and thrombosis are frequent causes of arterial obstruction.

Atherosclerosis is responsible for most cases of arterial occlusion affecting the myocardium, brain and peripheral arteries.

Arterial obstruction or narrowing causes a reduction in blood flow either during exercise or at rest. The clinical signs result from ischaemia. The

atherosclerotic lesions which affect large and small blood vessels in diabetics are very similar to those which appear in non-diabetics; however, they appear earlier, worsen more quickly and are more frequent in the case of diabetics.

Distal arterial occlusion below the knee together with microvascular alterations and neurological lesions are responsible for gangrene. The symptoms are intermittent claudication and pain at rest caused by ischaemia. Diabetic foot, which is caused by a combination of vasculopathy, neuropathy and infection, is one of the most dangerous complications of diabetes, and is the cause of most amputations. Amputation of the foot or leg is five times as frequent in diabetics as in non-diabetics. Angina and myocardial infarction are the most frequent complications of occlusion or stenosis of the coronary artery.

These local actions, together with those of the autonomic nervous system and the vascular system, cause vasoconstriction when activated, such as after exposure to cold; conversely, a reduction in these effects results in vasodilatation.

The development of collateral circulation which results from stenosis or a major obstruction of the arteries influences the degree of ischaemia. Some collateral vessels are present in normal tissue, but do not dilate until arterial obstruction appears, while other capillaries develop in weeks or months. The adrenergic nerves, which are part of the autonomic nervous system, are responsible for vasoconstriction or dilatation of the collateral vessels in response to the increase in arterial pressure, with the result that the flow of blood to the tissue is improved.

Substances produced by the endothelial cells which induce new blood vessel formation (neoangiogenesis) and vasodilatation were recently discovered. The production of VEGF (Vascular Endothelial Growth Factor), which seems to be responsible for the majority of the angiogenic and vasodilatory effect that results from stenosis or arterial obstruction, appears to

be particularly important.

Experiments with isolated animal muscles have demonstrated that continuous electrical stimulation for 5 days (stimulation of 0.3 ms of amplitude, frequency of 150 Hz and voltage of 0.1 V) increases VEGF production, the number of capillaries and the blood flow (Kanno S, Odam Abe M. Circulation 1999; 99, 2682-87).

Although the experiments described above seem to suggest that electrical stimulation of the muscles has beneficial effects on the circulation, the problem remains of how to induce a prolonged stimulation on nerves and muscles in humans.

Patients suffering from acute ischaemia or initial infarction present increased production of VEGF in the myocardium and in the endothelial cells of the capillaries and arterioles (Lee SH, Wolf PL, Escudero R, N. Engl. J. Med. 2000; 342, 626-33).

The revascularisation induced by a transmyocardial laser with the aim of reducing angina pain is accompanied by an increase in VEGF and angiogenesis (Horvath, Chiu E, Maun AC, Annals of Thoracic Surgery 1999; 68, 825-29).

Modern technology offers some highly sophisticated instruments which allow the use of new techniques such as transmyocardial laser revascularisation, but the results are still limited. An electrical phoryngeal neuromuscolar stimulator is disclosed in WO 99/24111.

The treatment of peripheral vascular disease is usually unsatisfactory. Vasodilators have a modest effect, and sympathectomy is ineffective. The injection of VEGF produced by GMO (Genetically Modified Organisms) is not without side effects. The only therapeutic solution is vascular surgery.

In practice, no really effective system for the treatment of peripheral vascular disorders has yet been found. Vasodilators give poor results, treatment with VEGF based on recombinant DNA is not safe enough, and even surgery is just one of the various alternatives, which has not demonstrated any real

efficacy.

The present invention proposes an apparatus for the treatment of ischaemic disease which can generate and apply a series of controlled pulses designed to stimulate the patient and elicit an effective response, which eliminates inflammation from the part of the body treated, activates the peripheral microcirculation and stimulates VEGF production.

The apparatus in accordance with the invention uses a non-invasive technique, because the stimulus is transmitted transcutaneously by means of electrodes.

The signals emitted by the machine are sent to the vascular receptors where they induce vasodilatation and stimulate VEGF release.

Using the apparatus in accordance with the invention, ischaemia can be treated and ischaemic pain reduced.

The invention is based on a series of studies conducted by the applicants which demonstrate that by applying a series of electrical pulses to the patient, a biochemical response can be induced which not only eliminates inflammation from the part of the body treated and reduces or eliminates pain, but also has a rapid muscle-relaxant effect, and stimulates vasodilatation and VEGF production.

However, the apparatus must also detect the response of the tissues to electrical stimulation and vary the stimulation parameters to obtain the desired result.

For this purpose, the apparatus to which the invention relates generates electrical pulses whose variables activate the patient's neurophysiological control systems.

The pulse parameters are defined on the basis of the bioreaction of the tissues. The intensity of the pulse is directly regulated by the patient, according to preset treatment programs.

After establishing experimentally that the apparatus in accordance with the invention produces excellent results with muscle relaxation, the inventors formulated the hypothesis that the same apparatus might effectively induce vasodilatation and stimulate VEGF production.

Subsequent experiments demonstrated that this hypothesis was well-founded, and that the apparatus to which the invention relates produces the postulated results.

The apparatus according to the invention comprises:

- means designed to generate electrical pulse series having a width from 10 to 40 μsec and intensity from 100 to 170 μAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec. and a voltage up to 220 Volts;
- means designed to apply the said pulses to a patient through the epidermis;
- means designed to evaluate the tissue reaction;
- means designed to vary the said pulses on the basis of the tissue reaction detected;

at least one of which means can be controlled by the patient/user.

The invention also provides a method of the treatment of vascular and/or muscle and/or tendon disorders, comprising:

a) applying to a patient in need thereof, a shies of electrical pulses having a width from 10 to 40 μsec and intensity from 100 to 170 μAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec. and a voltage up to 220 Volts trough electrodes located on the epidermis of the area to be treated;

b) detecting the tissue reaction after the application of the pulses;

c) modifying the width and intensity of the pulses in relation to the tissue reaction detected in point b).

The invention also provides a method for increasing the VEGF in a patient in need thereof, comprising:

a) applying to a patient in need thereof, a shies of electrical pulses having a width from 10 to 40 μsec and intensity from 100 to 170 μAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec. and a voltage up to 220 Volts trough electrodes located on the epidermis of the area to be treated;

b) detecting the tissue reaction after the application of the pulses;

c) modifying the width and intensity of the pulses in relation to the tissue reaction detected in point b).

Advantages features of the apparatus of the invention are stated in the annexed dependent claims.

One embodiment of the apparatus is illustrated in the attached figures, in which:

- figure 1 is a block diagram of the apparatus in accordance with the invention
- figure 2 is the circuit diagram of the forward/back selector switch in the circuit shown in figure 1
- figure 3 is the circuit diagram of the selector switch-counter logic network of the circuit shown in figure 1
- figure 4 is a diagram of the up/down circuits, + DAC
- figure 5 is the circuit diagram of the output stage of the circuit shown in figure 1
- figure 6 is the circuit diagram of the timer in the circuit shown in figure 1
- figure 7 is the circuit diagram of the automatic pulse train width regulator in the circuit shown in figure 1
- figure 8 is the circuit diagram of the frequency regulator and timer in the

circuit shown in figure 1

- figure 9 is the circuit diagram of the control activated by the patient in the circuit shown in figure 1;
- figure 10 shows the oscilloscopic trace of a pulse which shows a peak having a width of 10 nanosec.
- figure 11 shows the waveform displayed by an oscilloscope, of the pulse of fig. 10, over a total time of 100 nanosec.;
- figure 12 is an expanded view of the peak of the pulse of fig. 11.

The circuits illustrated in the figures do not require a more detailed explanation because the information obtainable from the drawings is sufficient to allow an expert in the field to implement the invention.

The apparatus includes devices which generate and regulate a series of electrical pulses that are sent to a pair of electrodes at the output, and is fitted with a control which allows the patient to regulate at least one of the control parameters of the said pulses, especially the voltage, according to preset treatment programs correlating the detected bioreaction to the time, frequency and width of the electrical pulses.

The electrodes, one active and one passive (or reference) electrode, are applied in different positions, depending on the tissue treated.

These regulations can be performed by means of an ordinary control fitted with pushbuttons and/or potentiometers which is activated by the patient.

The circuit shown in figure 2 allows forward/back regulation, in that it allows the patient to select an increased or reduced voltage, while the circuit shown in figure 3 is a counting circuit which counts the number of steps set with the control, in order to calculate the extent of the variation to be imparted to the output voltage signal.

In particular, the amount of this voltage variation is between 0.47 and 0.63 volts.

The digital count signal output from circuit 3 is then converted into an analog signal in the circuit shown in figure 4, where the pulse trains are generated; they then pass to the output stage shown in figure 5 after being suitably regulated by the circuits shown in figures 6, 7 and 8.

The circuits shown in figures 6 and 7 regulate the duration (width) of the pulses and the increase in width between two successive pulse trains.

The circuit shown in figure 8 is the timer which determines the duration of the pulse train, while figure 9 shows the circuit diagram of the control activated by the patient.

During the initial stage of the experiments, the apparatus was regulated so as to generate a series of pulses with a voltage of approx. 80 volts, the width of each pulse being selectable between 10 and 90 microseconds, and the frequency being selectable between 1 and 999 pulses a second.

The electrodes at the output of the apparatus were applied to the epidermis at the area to be treated, one to the motor point and the other to the muscle belly.

The tests were performed by effecting treatments of different frequencies ranging from 1 to 420 pulses a second, and different widths, ranging from 10 to 50 microseconds, for a total time of 10 to 15 minutes.

120 patients suffering from orthopaedic disorders whose main component was local ischaemia or inflammation were treated.

The results demonstrated good vascularisation of the tissues, but there was no significant improvement in the inflammation.

The pulses were checked with an oscilloscope, which showed that the pulse in contact with the skin underwent considerable deformation, and the patient developed evident tolerance after only 3 minutes.

During a second series of tests, the machine was set to vary the width of the pulses after each series of pulses applied in the same cycle, in order to

prevent tolerance by the patient and deformation of the pulses.

300 patients suffering from orthopaedic disorders complicated by inflammation and ischaemia were treated by applying several series of pulses and increasing the pulse width from time to time during the same treatment.

The results demonstrated that reduction of inflammation and improvement in blood flow were associated with modulation of the neurovegetative nervous system.

A further test was then conducted with 120 patients suffering from orthopaedic disorders associated with inflammation or deficiency of the local microcirculation.

The treatment comprised 12 ten-minute sessions in which electrodes were applied to the epidermis at a distance of approx. 10-15 centimetres apart.

The patient could increase or decrease the voltage of the pulse during stimulation with a remote control.

The variation in intensity of the pulse voluntarily decided on by the patient and the variation in the physiological bioreaction time or muscle relaxation times were observed simultaneously with a double-trace oscilloscope.

These first tests confirmed the inventor's intuition, namely that the application of series of electrical pulses under given voltage, frequency and width conditions could produce the desired results.

The following examples and tables show the results of further, more detailed tests.

Example 1

Muscle relaxation (Tables 1a-d and 2)

With the machine in accordance with the invention, one electrode was applied to the motor point and one to the belly of the trapezius muscle, and pulse trains were sent to the patient for 30 seconds at a voltage of approx. 180

volts, with a frequency of one pulse a second and a width of 10 microseconds.

During the second phase, lasting 5 seconds, the pulses were applied at the frequency of one a second, with a width of 20 microseconds.

As the test continued, the parameters were varied from time to time as indicated in the annexed tables 1a to 1d until the muscle reached spasm, then relaxed and remained in that condition.

As will be seen from the graph in Table 2, after approx. 12 phases of treatment the muscle reached an almost permanent state of relaxation.

This relaxation corresponds to the maximum degree of vascularisation and the maximum anti-inflammatory effect.

The anti-inflammatory treatment programme is shown in Table 3 and the associated Graph 4.

Table 5 and the associated graph 6 show a treatment programme for activation of the microcirculation.

The details set out above demonstrate that the apparatus in accordance with the invention is able to relax the muscles, induce vasodilatation, increase the blood flow and stimulate new vessel production.

The technique is non-invasive because the signal is transmitted transcutaneously through electrodes.

The signals emitted with this new technology are conducted by the sensory and proprioceptive fibres of the autonomic nervous system, and reach the vascular and muscle receptors through which vasodilatation and muscle relaxation is produced; the blood flow is increased and VEGF release is stimulated.

The treatment combats ischaemia and reduces pain. The clinical symptoms of ischaemia, such as claudication due to contraction of the calf, thigh or buttocks and pain at rest, rapidly regress, and the patient walks normally.

Vasodilatation and increased blood flow take place in all parts of the body to which the treatment is applied. The effect is long-lasting; however, its duration depends on the degree of arterial obstruction and the time taken for collateral circulation to develop. Measurements taken with a laser doppler demonstrate significant increases in blood flow in the treated areas.

The efficacy of the treatment is demonstrated by the following example.

Example 2

12 patients with distal arterial occlusion (7 with occlusion of the tibial artery and 5 with occlusion of the femoral artery) were studied before, during and after stimulation with the new technology.

The VEGF (pg/ml) was assayed at the times shown in figure 10.

As will be seen, an increase in VEGF was already evident 2-3 minutes after the start of the stimulus; it peaked after 5 mins (the increase was approx. 50%), and returned to normal after 15 mins.

Further tests confirmed that the best results can be obtained with series of pulses having a width from 10 to 40 μsec. and an intensity from 100 to 170 μAmp., with a peak having a width from 7 to 12 nanosec. and a voltage up to 220 Volts.

The waveform of a pulse of this kind, as displayed by an oscilloscope, is shown in figgs. 10-12.

These data demonstrate for the first time that the application of the invention is able to increase VEGF, the most potent specific endogenous angiogenic factor identified to date. Increased VEGF production was also accompanied by vasodilatation. By contrast with what happens in laboratory animals subjected to a direct stimulus on the isolated muscle and nerve, this method enables the stimulus to be induced through the skin with electrodes. The time taken to stimulate VEGF is a few minutes, whereas the electrical stimulation used in animals takes days to achieve the same result. In the case of

severe stenosis or arterial obstruction, recurrence of the ischaemia symptoms after suspension of the treatment is often due to a deficiency in the development of collateral circulation. In this case the treatment must be continued or an arterial bypass performed, which may be followed by new treatment to ensure complete healing of the tissues.

Maintenance of a high blood flow in the treated tissues increases the trophism of the tissue, prevents necrosis and heals ulcers.

The application of this invention to specific parts of the body rather than directly to the heart induces coronary vasodilatation and increases VEGF production in the coronary sinus.

This effect has been observed in 3 patients who underwent cardiac catheterisation, from whom blood samples were taken at the same time to assay the cardiac VEGF.

The treatment can also be applied to lesions of the spinal column and pain syndromes of the back and neck.

The spinal column, together with the spinal cord, nerve roots, spinal ligaments and paraspinal muscles are the sites of some of the most frequent disorders to which human beings are liable. The cervical and lumbar pain which originates in these structures affects nearly everyone sooner or later. This disorder, together with alcoholism, is one of the major causes of absenteeism.

The most important symptom of lesions of the spinal column and the various structures that compose it is pain, which may be local or muscle-related. Pain is caused by irritation of the nerve ending at the site of the pathological process. Treatment of patients with cervical and back pain is very difficult, and often ineffective. Rest, combined with analgesics, is currently considered to be the best treatment. Physiotherapy is performed with the aim of strengthening the paravertebral muscles to prevent painful relapses. Neck

manipulation is potentially dangerous. This invention provides an innovative approach to the treatment of lesions of the spinal column.

As mentioned, this new technology acts through the autonomic nervous system, targeting the structures of the spinal column which are most often affected by painful disorders, such as the ligaments, periosteum and paravertebral muscles, by acting on the muscle spindles, the Golgi tendon organs and the joint proprioceptors. Its action is followed by a reduction in oedema, inflammation and pain.

This treatment has been tested on some 200 patients suffering from cervical or lumbar pain.

Most of the patients felt better within a few days (3-10). 60 of them had a slipped disc; 10 of them had already been operated on for slipped disc but still felt pain. The treatment was effective in 92% of cases. 90% of the patients suffering from slipped disc did not need an operation because the compression or inflammation symptoms of the nerve root were eliminated by the treatment.

The results obtained with this method demonstrate that the technique has multiple effects on mechanical lesions of the spinal column and their complications:

- it eliminates pain and returns the proprioceptive sensitivity to normal
- it restores normal muscle contractility
- it eliminates inflammation.

The same technology has been tested in other disorders.

For example, the invention has been successfully tested in the treatment of numerous other disorders such as cervical, back, hip, thigh and knee pain, knee instability, Achilles tendinitis, calcaneal spur, metatarsalgia, and shoulder, elbow, wrist and hand disorders.

In conclusion, the new treatment improves the quality of life and reduces one of the most frequent causes of absenteeism.

CLAIMS

1. Apparatus for the treatment of vascular and/or muscle and/or tendon disorders and/or to increase the production of VEGF, comprising:

- means designed to generate electrical pulse series having a width from 10 to 40 μsec and intensity from 100 to 170 μAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec. and a voltage up to 220 Volts;
- means designed to apply the said pulses to a patient through the epidermis;
- means designed to evaluate the tissue reaction;
- means designed to vary the said pulses on the basis of the tissue reaction detected;

at least one of which means can be controlled by the patient/user.

2. Apparatus for the treatment of vascular and/or muscle and/or tendon disorders as claimed in claim 1.

3. Apparatus as claimed in each of the preceding claims, wherein the voltage of the pulses applied is controlled by the patient/user by suitable means.

4. Apparatus as claimed in each of the preceding claims, characterised in that it includes a pair of electrodes designed to transmit the said pulses, one of which can be applied to the motor point and the other to the muscle belly in the area to be treated.

5. Apparatus as claimed in each of the preceding claims, characterised in that the said means designed to transmit the said pulses include devices able to vary the voltage, amplitude and frequency of the said pulses.

6. Apparatus as claimed in each of the preceding claims, characterised in that it includes means designed to regulate the amplitude and frequency of the

pulses, which said means are activated directly by the patient.

7. Apparatus for the treatment of muscle contraction as claimed in claim 1, characterised in that it includes a pair of electrodes designed to transmit the said pulses, one of which can be applied to the motor point and the other to the muscle belly in the area to be treated.

8. Apparatus for anti-inflammatory treatment as claimed in claim 1, characterised in that it includes an active electrode designed to be applied at the site of inflammation, and a passive electrode external to the said site.

9. Apparatus for the treatment of vascular disorders as claimed in claim 1, characterised in that it includes an active electrode designed to be applied upstream of the occlusion and a passive electrode designed to be applied downstream thereof.

10. Apparatus for the activation of the microcirculation as claimed in claim 1, characterised in that it includes an active electrode designed to be applied at the ischaemic site and a passive electrode designed to be applied close to the venous plexus.

11. Apparatus as claimed in claim 1, characterised in that it includes means designed to vary the voltage of the pulses applied, with variable increments between 0.47 V and 0.63 V for each step of the up/down circuit.

12 Apparatus as claimed in claim 1, characterised in that it includes means designed to vary the number of pulses applied between 1 and 420 Hz/second.

13. Apparatus as claimed in claim 1, characterised in that it includes means designed to vary the width of the pulses between 10 and 50 μsec.

14. A method of the treatment of vascular and/or muscle and/or tendon disorders, comprising:

a) applying to a patient in need thereof, a shies of electrical pulses having a width from 10 to 40 μsec and intensity from 100 to 170 μAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec. and a

voltage up to 220 Volts trough electrodes located on the epidermis of the area to be treated;

b) detecting the tissue reaction after the application of the pulses;

c) modifying the width and intensity of the pulses in relation to the tissue reaction detected in point b).

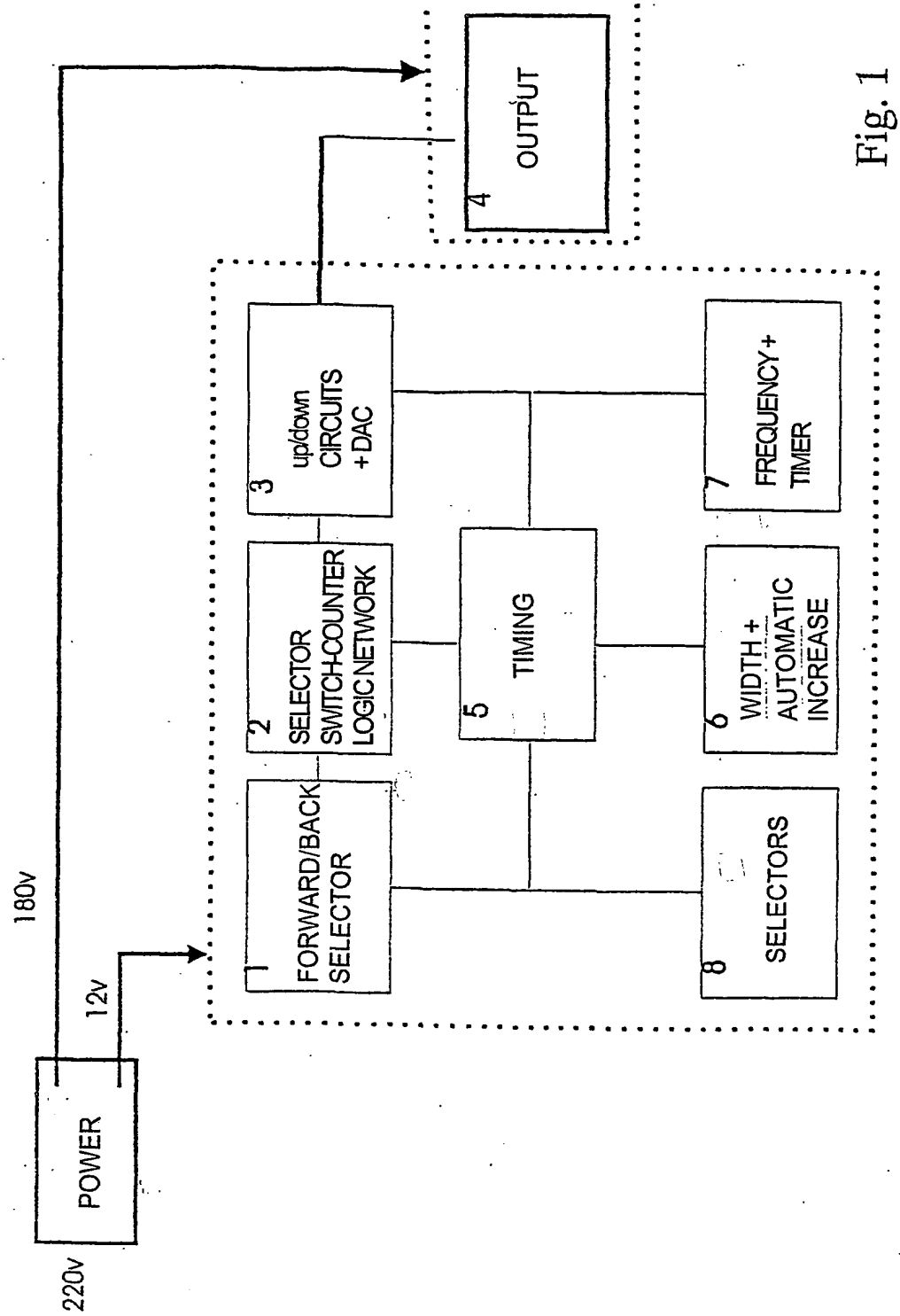
15. A method according to claim 14 wherein the pulses are modified according to preset treatment programs correlating the detected bioreaction to the time, frequency and width of the electrical pulses.

16. A method for increasing the VEGF in a patient in need thereof, comprising:

a) applying to a patient in need thereof, a shies of electrical pulses having a width from 10 to 40 μsec and intensity from 100 to 170 μAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec. and a voltage up to 220 Volts trough electrodes located on the epidermis of the area to be treated;

b) detecting the tissue reaction after the application of the pulses;

c) modifying the width and intensity of the pulses in relation to the tissue reaction detected in point b).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180v
12v
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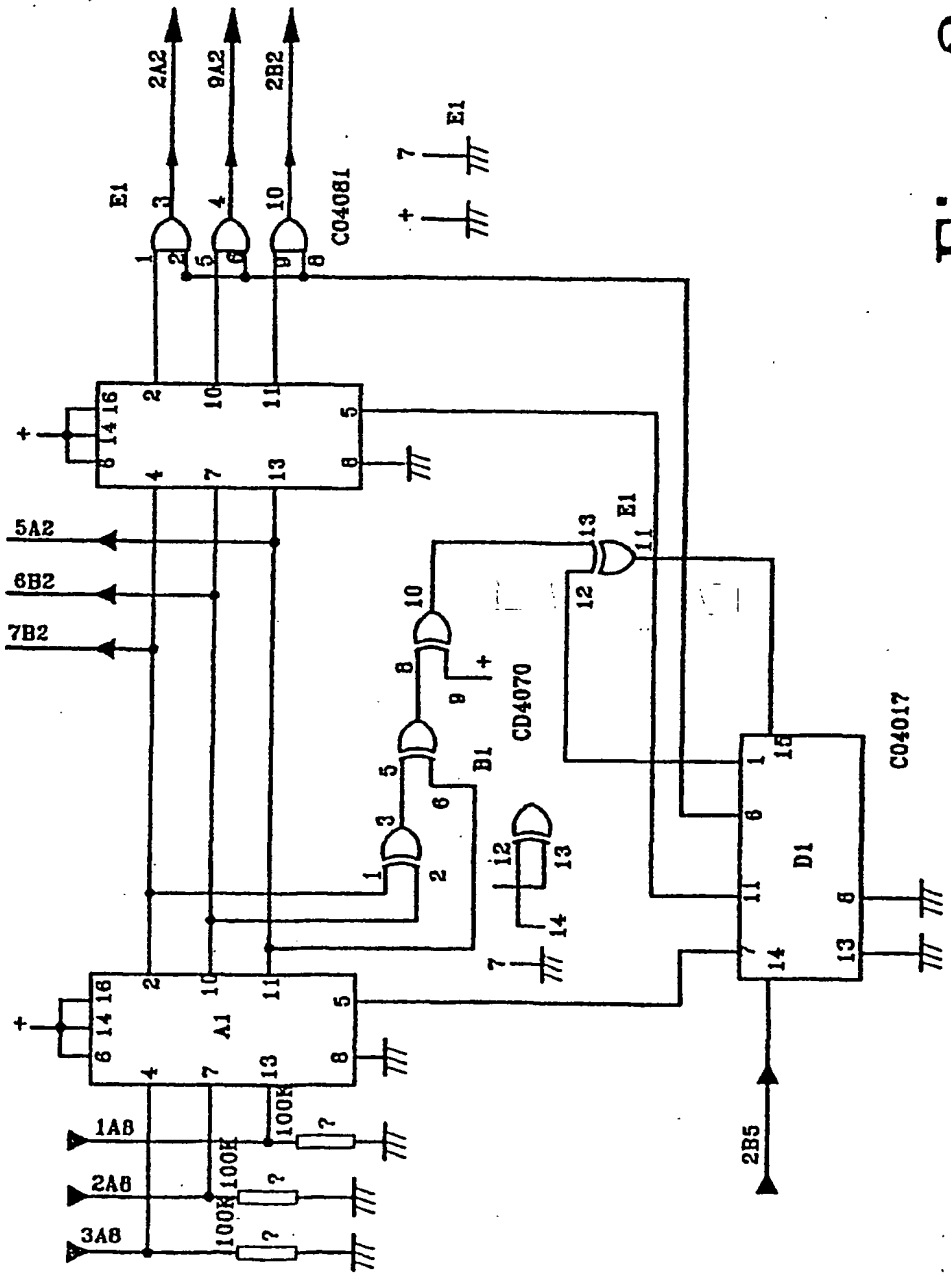
2 SELECTOR SWITCH-COUNTER LOGIC NETWORK
3 up/down CIRCUITS +DAC
4 OUTPUT
5 TIMING
6 WIDTH + AUTOMATIC INCREASE
7 FREQUENCY+ TIMER
8 SELECTORS

Fig. 1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100K
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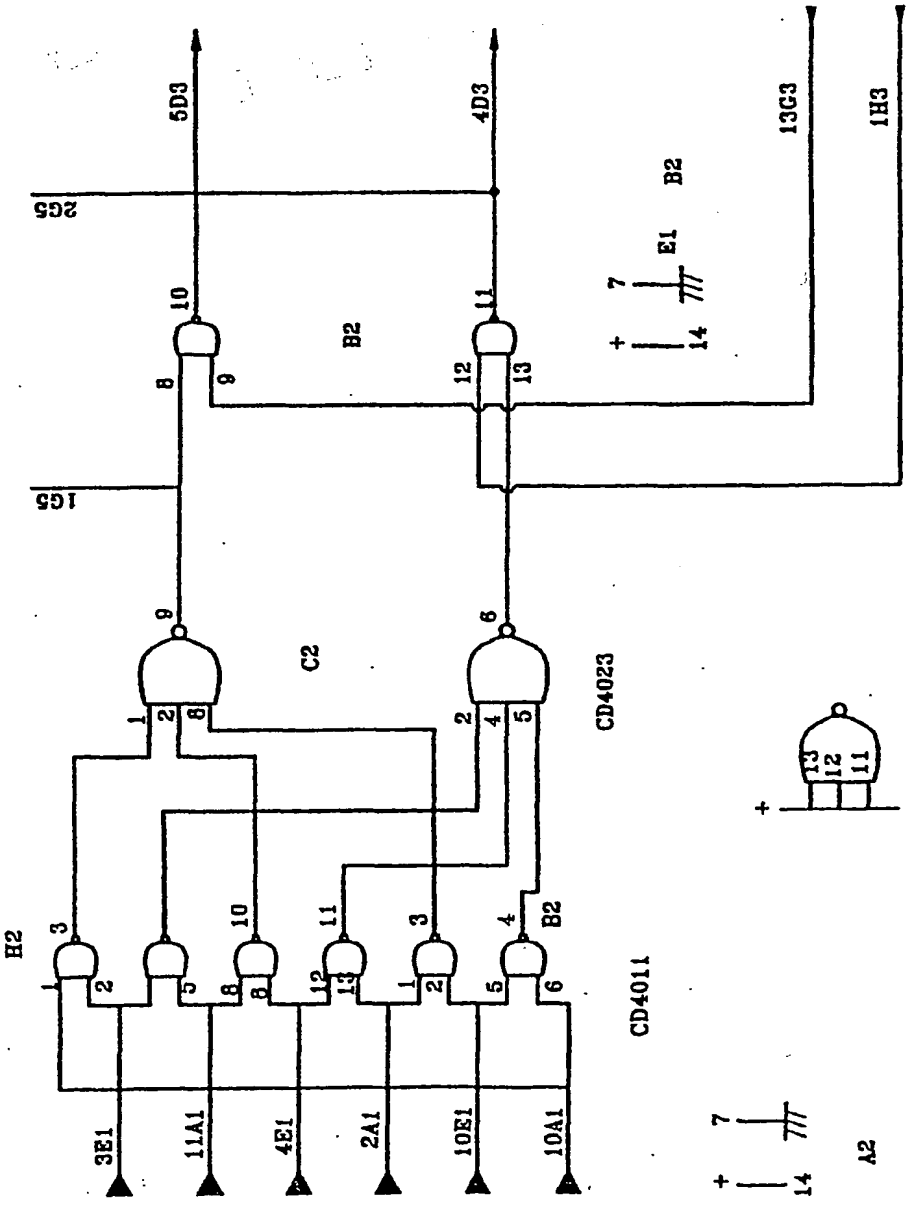
Fig. 2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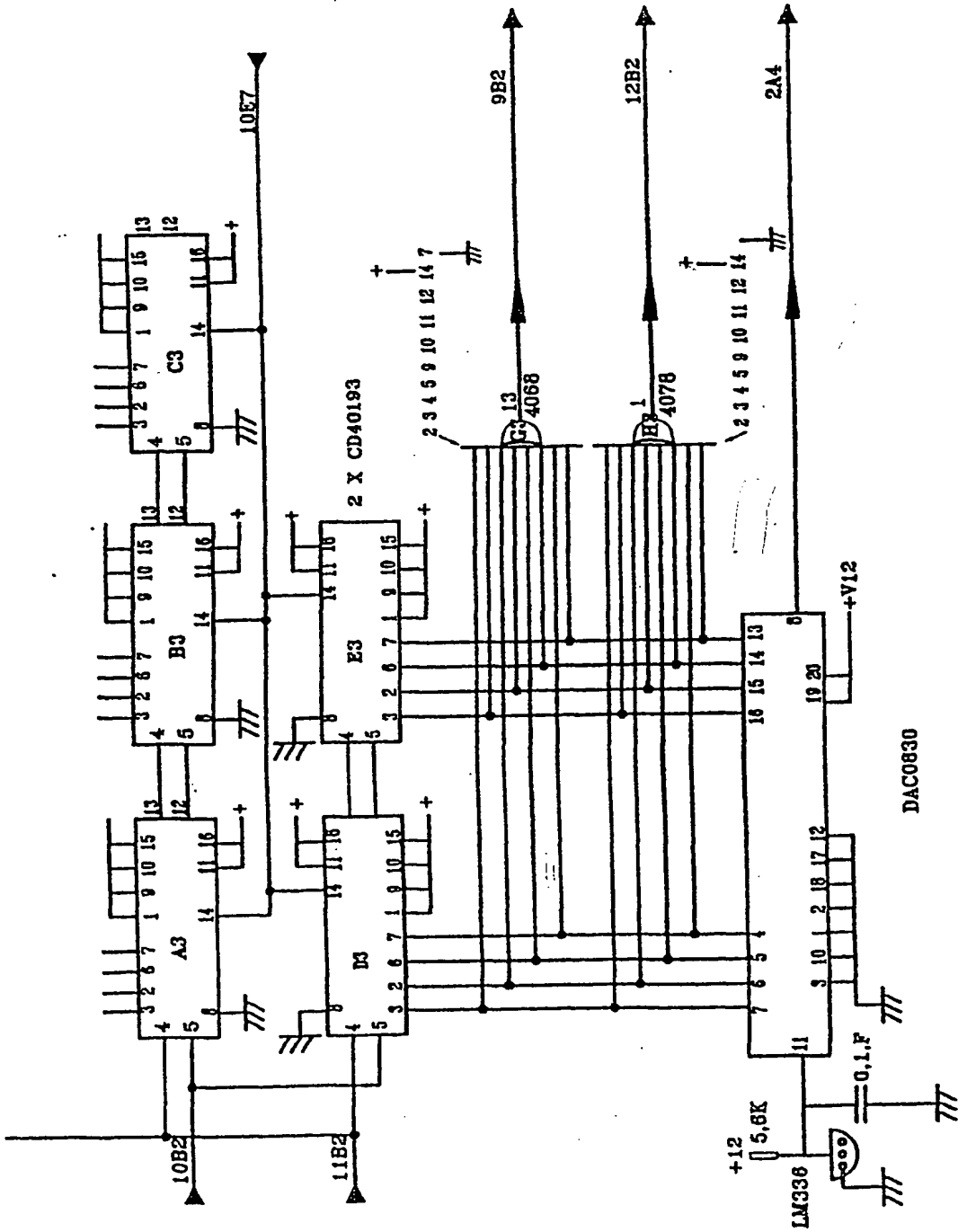
2A1
10E1
10A1
A2

Fig. 3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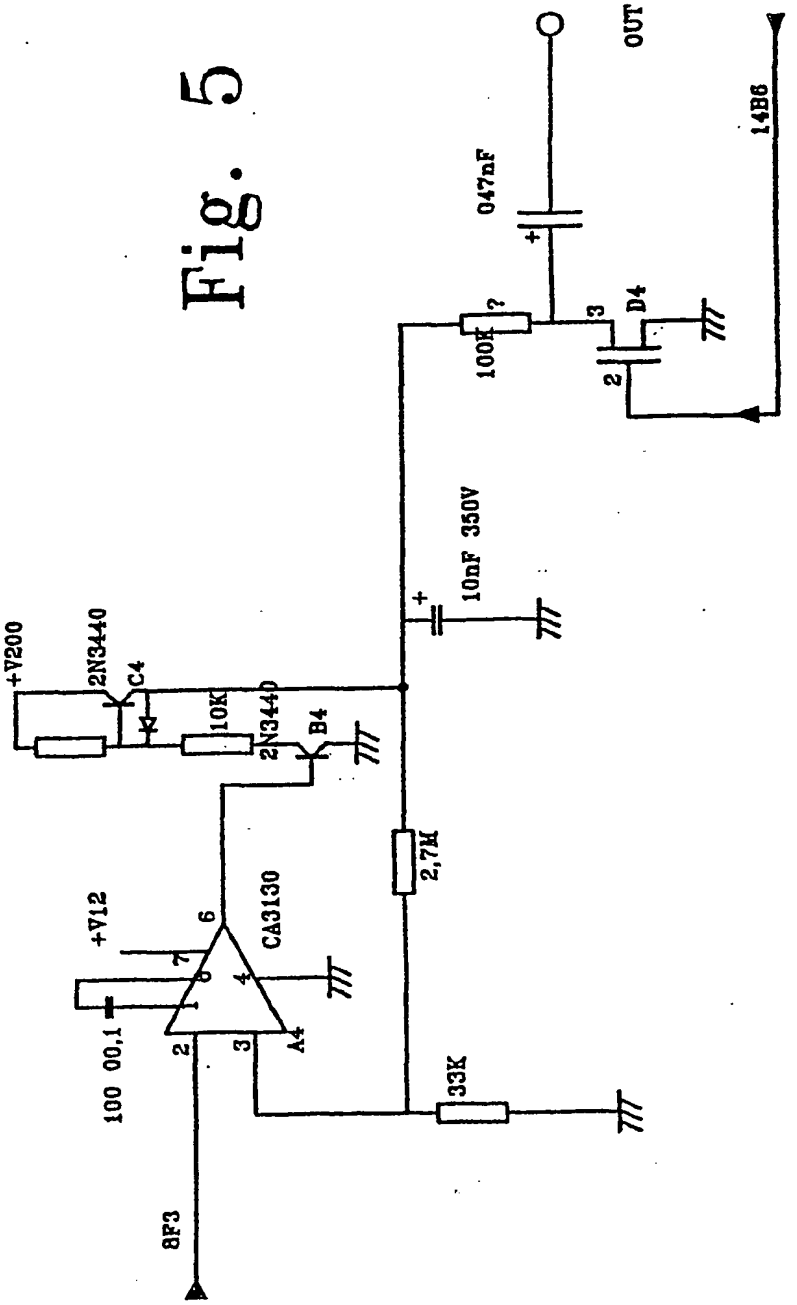
LM336
C3
B3
E3
A3
D3

Fig. 4

Fig. 5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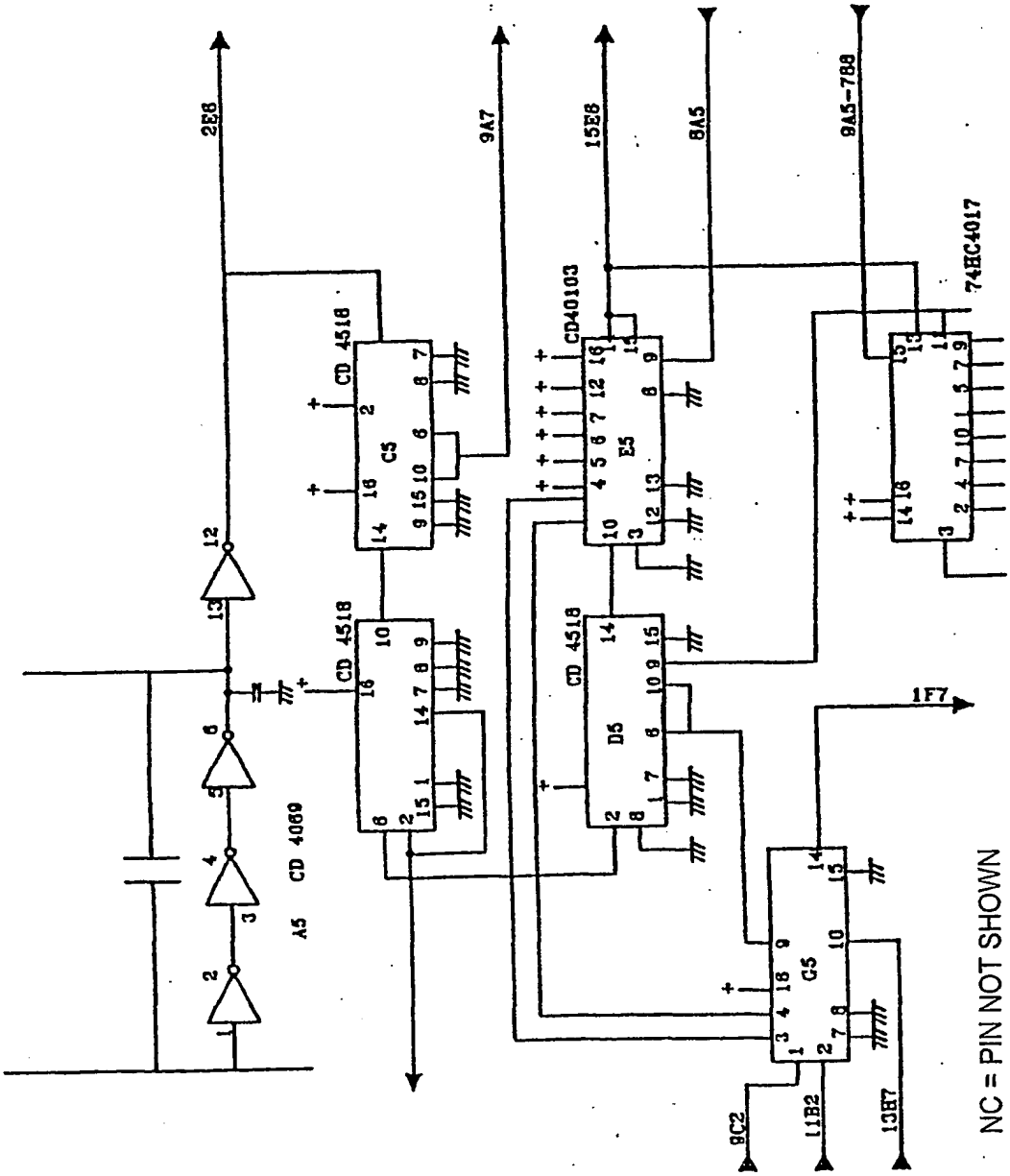
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CD 4518
C5
CD40103
E5
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D5
1F7
8C2
11B2
13E7
NC = PIN NOT SHOWN

Fig. 6

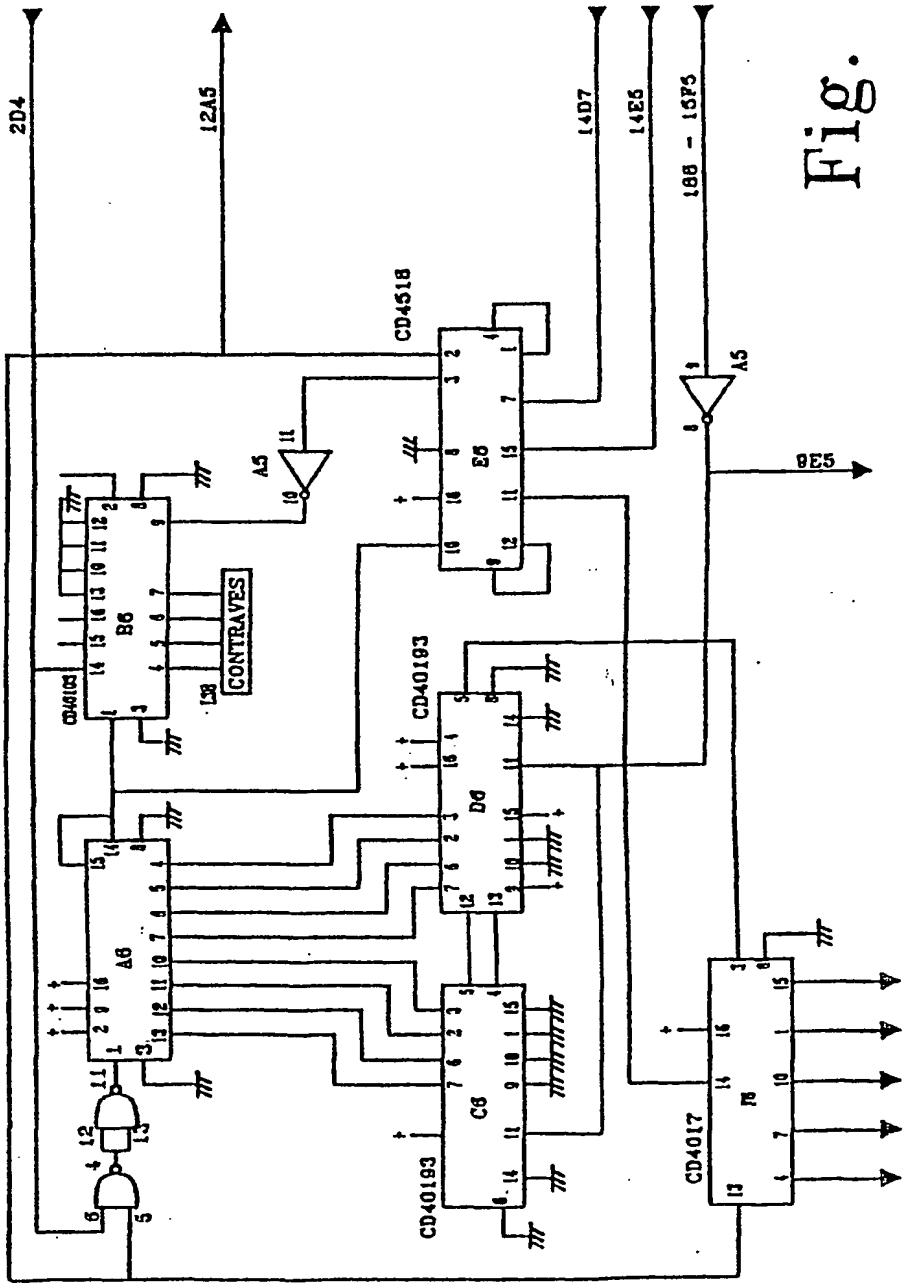
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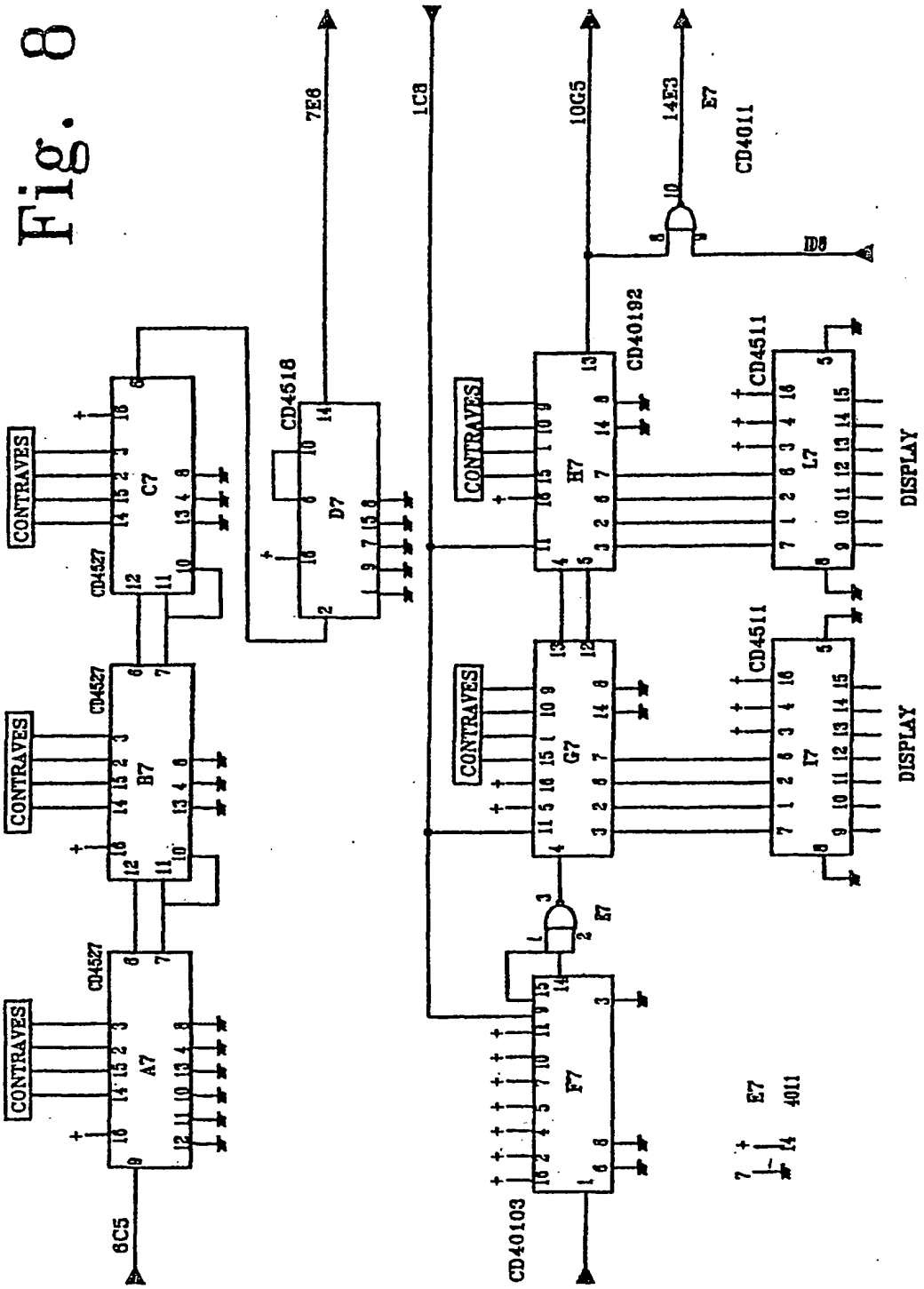
Fig. 7

Fig. 8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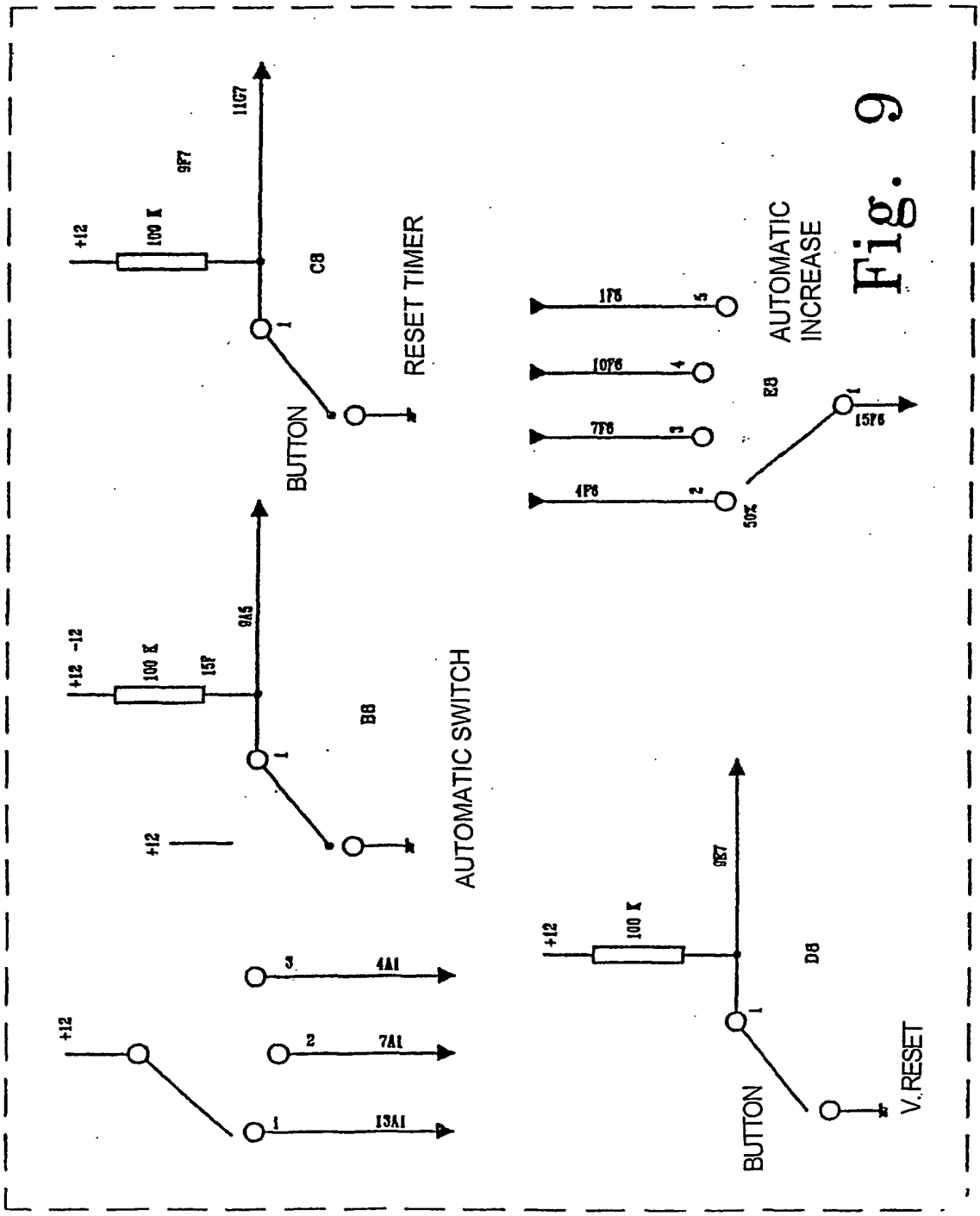
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9F7
11G7
C8
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BUTTON
+12 -12
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15F
9A5
B8
+12
AUTOMATIC SWITCH
3
4A1
2
7A1
1
13A1
1F6
10F6
7F6
4F6
E8
AUTOMATIC INCREASE
15F6
+12
100 K
9B7
D8
BUTTON
V.RESET

Fig. 9

Fig. 10

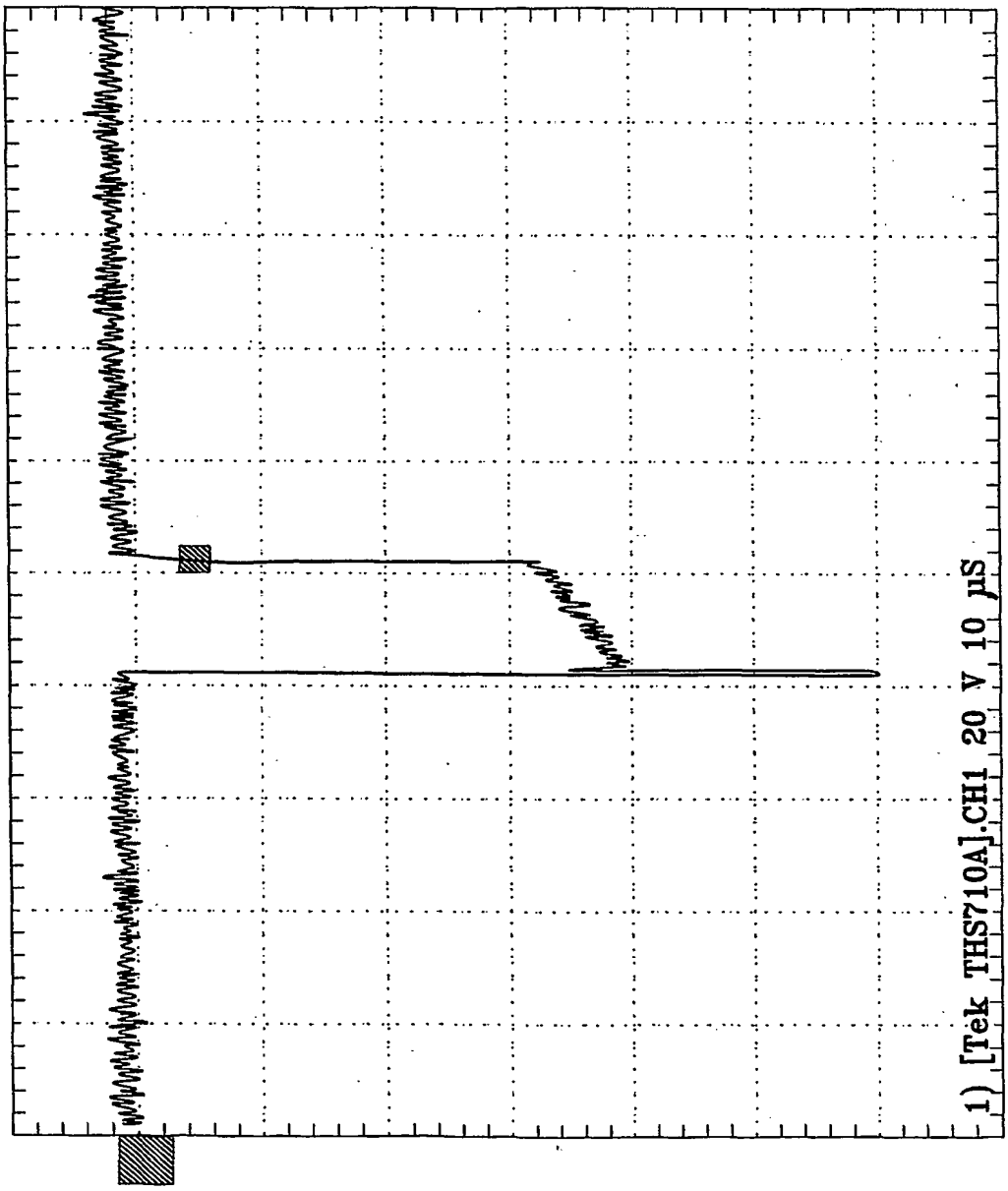


Fig. 11

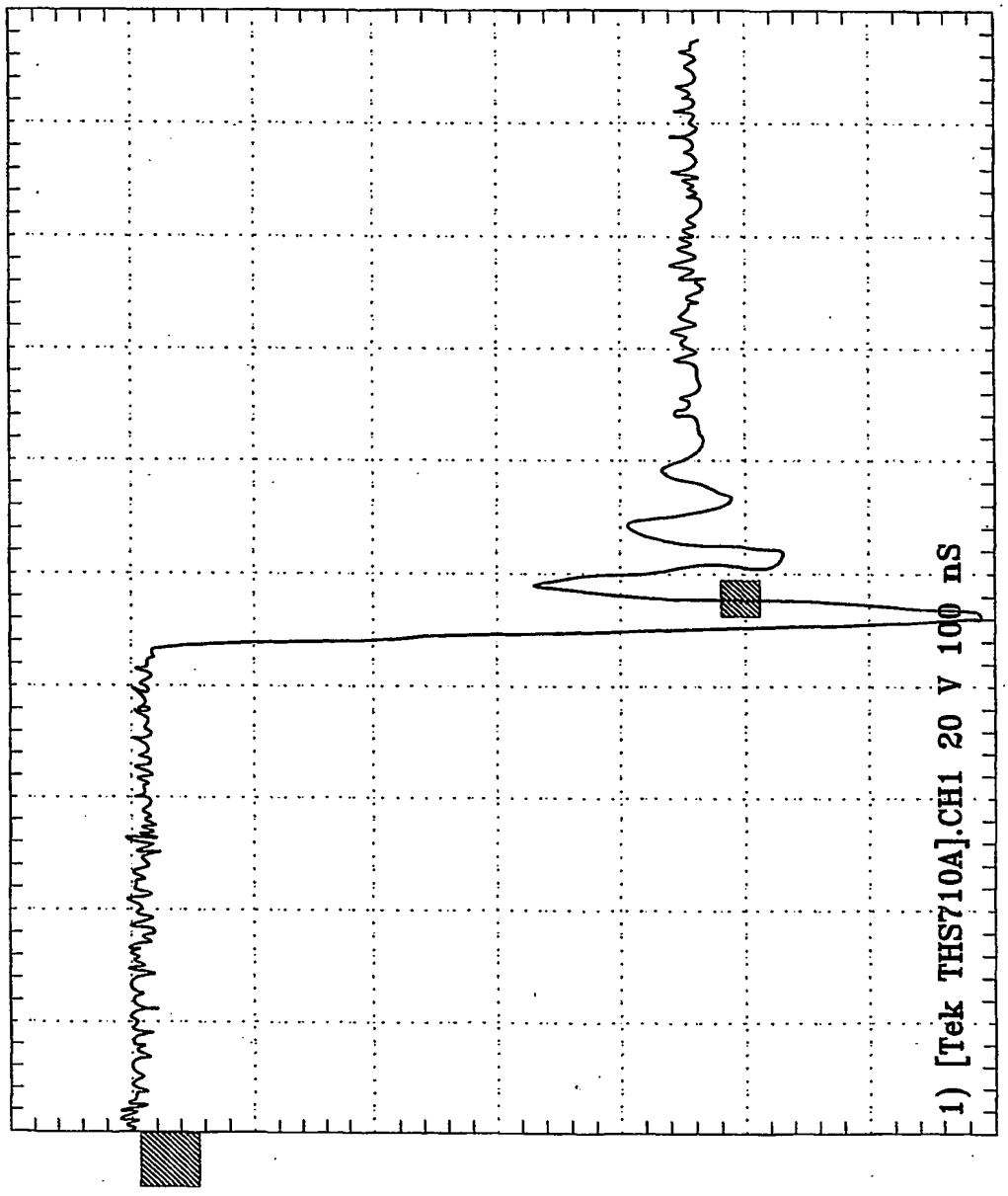
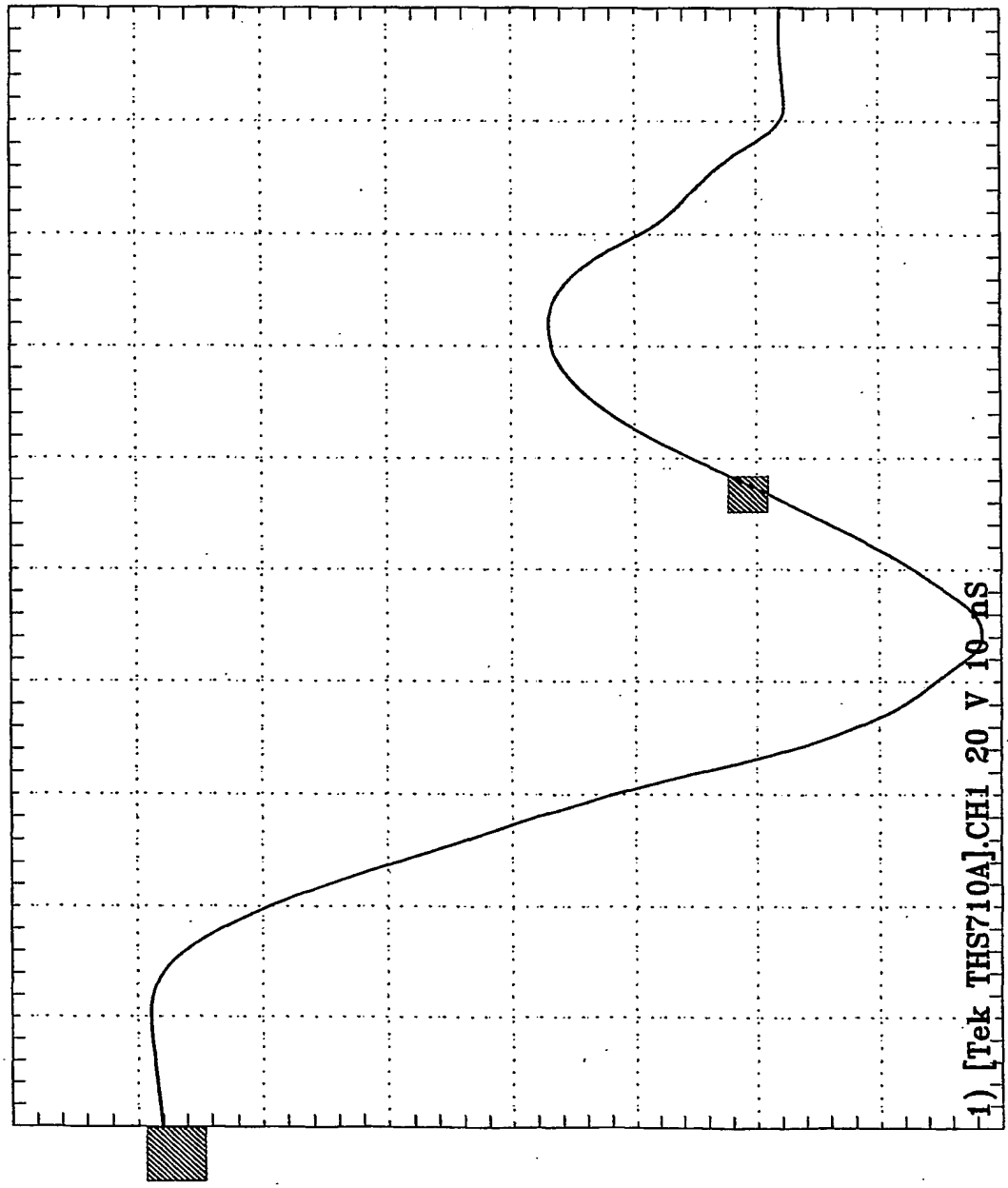


Fig. 12



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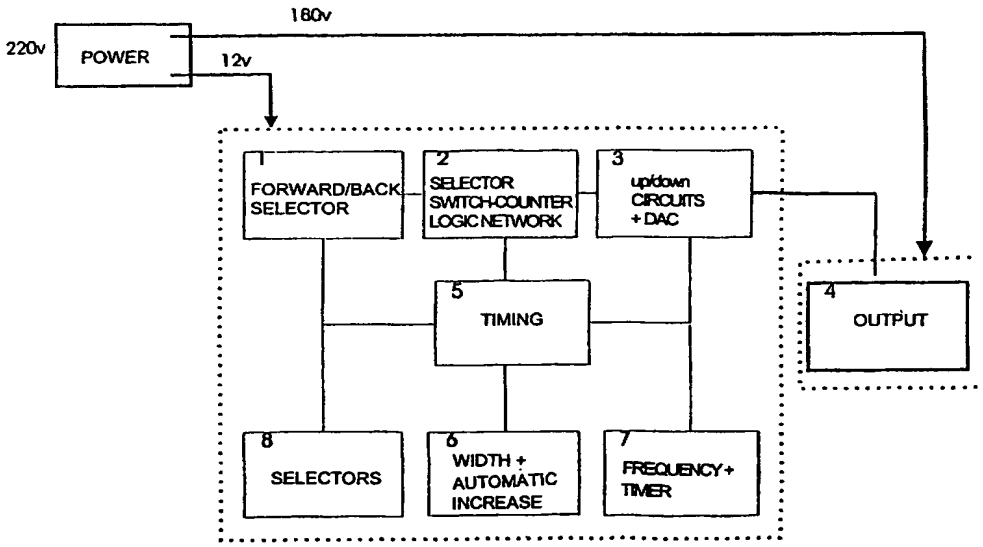
(54) Title: APPARATUS FOR THE TREATMENT OF VASCULAR AND ORTHOPEDIC DISORDERS BY APPLICATION OF ELECTRICAL PULSES TO THE SKIN TO MODULATE THE NEUROVEGETATIVE SYSTEM



(57) Abstract: An apparatus for the treatment of vascular and/or muscle and/or tendon disorders and/or to increase the production of VEGF, comprises: means designed to generate electrical pulse series having a width from 10 to 40 usec and intensity from 100 to 70 uAmp, wherein each pulse has a peak that has a width from 7 to 12 nanosec, and a voltage up to 220 Volts; means designed to apply the said pulses to a patient through the epidermis; means designed to evaluate the tissue reaction; means designed to vary the said pulses on the basis of the tissue reaction detected; at least one which means can be controlled by the patient/user.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.